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EXAMINER: DAVIS, M

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ART UNIT	PAPER NUMBER
1806	59

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 8/2/97, paper #57

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 (month(s)), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 19, 62-79 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 19, 62-79 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-421-632/40206

The finality of the previous Office action has been withdrawn, and the prosecution of this application is reopened to include art not previously cited.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 19, 62-79 are being examined.

The following rejections are withdrawn: 1) Rejection of claim 72, under 35 USC 112, first paragraph, in view of applicant's arguments, 2) Rejection under 35 USC 102/103 of claims 19, 62, 65, 67-68, 71, 73-79, which is replaced by a new rejection under 35 USC 103 of claims 19, 62-79.

REJECTION UNDER 35 USC 102

Rejection under 35 USC 102 of claim 62 pertaining to anticipation by Real *et al.* remains for reasons already of record in paper No.52, and its supplemental No.54, and for reasons as follows:

Claim 62 is drawn to an isolated tumor antigen comprising Urinary Tumor Associated antigen (UTAA) subunit, which after reduction by beta-mercaptoethanol and separation by SDS-polyacrylamide gel electrophoresis, exhibits a molecular weight of about 90 to 100 kD. Applicant argues that claim 62, without the dependent claims reciting the ioselectric point and heat stability of the claimed UTTA , is not anticipitated by Real *et al.*. Applicant argues that despite the similarity in molecular weight, there are no other facts that indicate that the 90 kilodalton antigen,

which is present in melanoma cells, and in patient sera, as taught by Real *et al.*, is the same as the claimed Urinary Tumor Associated antigen. Applicant further argues that Real *et al.*'s antigen is present on but a few melanoma samples, whereas UTAA is found in most melanomas, most sarcomas, most neuroblastomas and most lung cancers.

Applicant's arguments set forth in paper No. 55 have been considered but are not deemed to be persuasive for the following reasons:

1. Claim 62 is not drawn to tissue distribution of UTAA.

2. The tissue distribution of the tumor antigen taught by Real *et al.* appears to be the same as the tissue distribution of the claimed tumor antigen UTAA. In the specification, third paragraph, page 13, UTAA is defined as "a high molecular weight glycoprotein that was initially detected in the urine of melanoma patients but subsequently found to occur in other body fluids as well." Thus, the 90 kD melanoma antigen, which is found in patient sera, as taught by Real *et al.*, is the same as the claimed UTAA, as defined by applicant, i.e. a 90 kD melanoma antigen found in body fluids of patients. Furthermore, although Real *et al.* do not teach that the 90 kD melanoma antigen also occurs in most sarcomas, most neuroblastomas and most lung cancers, this fact does not exclude that the 90 kD antigen taught by Real *et al.* could occur in other type of tumors, because it is possible that Real et al have not tested the presence of said 90 kD antigen in other tumors. The burden is on applicant to show that the 90 kD antigen taught by Real *et al.* does not occur in other tumors, besides melanomas.

3. Moreover, using a method similar to the claimed method for defining the molecular weight of UTAA, Real *et al.* subjects the precipitated 90 kD antigen to a reduction with dithiothreitol, and separation by SDS-gel electrophoresis (column 3, firt paragraph). Dithiothreitol has the same effect as beta-mercaptoethanol in reducing protein samples, and both reagents are used routinely, and interchangeably, in the art for gel electrophoresis.

Thus, without properties such as isoelectric point, and heat stability of dependent claims, the claimed tumor antigen UTAA from claim 62 by istself, reads on the 90 kD tumor antigen taught by Real *et al.*

Again, as mentioned in previous Office Action, paper No. 52, page 4, third paragraph, the examiner suggests that the properties of UTAA, which distinguish UTAA from Real's antigen should be incorporated into claim 62 to alleviate this 102 rejection.

ANSWERS TO APPLICANT'S ARGUMENTS AGAINST FORMER REJECTION UNDER 35 USC 102/103 OF CLAIMS 19, 62, 65, 67-68, 71, 73-79

Applicant argues that the reference does not enable the production of the claimed purified 90 kD melanoma antigen, UTAA, "given the lack of information on (i) parameters for effecting the isolation of UTAA" from urine, (ii) immunogical profile of UTAA, i.e. binding to a monoclonal antibody against UTAA, and (iii) the structure of UTAA.

1. In attached declarations, applicant argues that the Euhus et al. abstract would not be enabling for UTAA or for methods relating to diagnosis of melanoma using UTAA or UTAA

specific antibodies, because "key conditions such as the proper pH or ionic strength under which isolation was conducting are missing, as are the migration distances or retention times for gel or column purification". In other words, "what salt condition or ionic strength will result in elution of the antigen. As illustrated by the reference provided by the examiner, as salt gradient results in elution of different species at different ionic strength, but which one contains UTAA?". Furthermore, the gel filtration reference in Euhus et al. does not mention what type of dye ligand or the elution mechanism.

2. Thus the rejection is improper because it relies on the instant specification which breathes meaning and significance into the excerpted passsage.

3. In a second declaration, applicant argues that "the absence of a meaningful description of UTAA", i.e. amino acid sequence of UTAA, "or an antibody that recognises UTAA would preclude the skilled artisan from confirming that the work described by Euhus et al. had, in fact, been reproduced."

4. The rejections of the dependent claims are improper because these rejections are based on the premise that UTAA is available to the skilled artisan.

Applicant's arguments set forth in paper No. 55 have been considered but are not deemed to be persuasive for the following reasons:

1. Parameters necessary for the isolation of UTAA from urine.

As recited in prior Office action, paper No. 52, page 4 bridging page 5, a reference by Pharmacia Fine Chemical, 1980, teaches how to isolate proteins from an ion exchange column, a

method commonly used in the art. A continous salt gradient with a range of salt concentrations could be used for elution of different species of proteins, detected as different peaks, and thus the exact salt condition is not necessary for the elution of any protein. To detect which peak contains UTAA, one could use an autologous and allogeneic antibody in ELISA, as taught in the abstract, line 4-6, by Euhus et al. ELISA is a method of detecting protein using antibody, and is well known in the art. Furthermore, Euhus et al. refers to previous work which describes UTAA. In one of such previous work, Rote NS et al, 1980, J. Surgical Res. 29: 18-22, and the referred references 3, 4, and 6 (p. 18, column 1, first paragraph, and page 22, references section) teach tumor-associated antigens detected by autologous sera in urine of patients with solid neoplasms. Rote et al further teach that unlike other tumor-related urinary antigens, the antigens they observe induce a complement fixing antibody in the host, is heat stable at 100^0 C for 60 min, and "comprised of molecules of about 1 x 10^6 daltons which could be dissociated into smaller subunits by treatment with 6M urea. These subunits express approximately 50% of the antigenic activity " (page 21, bridging page 22).

Gel filtration is another method of protein isolation well known in the art. Another reference by a manual book published by Pharmacia Fine Chemical, 1980, which teaches how to isolate protein using gel filtration is enclosed. Pharmacia teaches that "the separation of proteins in gel filtration depends on the different abilities of the various sample molecules to enter pores which contain the stationary phase. Very large molecules which never enter the stationary phase, move through the chromatographic bed fastest" Smaller molecules are eluted in order of

decreasing molecular size" (page 4). The eluent is just a simple buffer solution, as shown in one example on figure 6, page 14. Furthermore, molecular weight standards are routinely used for calibrating the gel filtration column (pages 26-27). It is well known in the art that molecular weight standards could be easily tagged with dye ligands for color detection on the column.

2. Structure and immunological profile of UTAA.

The issue of lack of enablement, due to the absence of the amino acid sequence of UTAA in the abstract by Euhus et al., is improper, because it is well known in the art that proteins could be isolated without prior knowledge of their amino acid sequences. See for example, the isolation of a new endonuclease by Ljungquist, S, 1977, JBC, 252(9): 2808-2814.

Moreover, as recited in the previous Office action, paper No. 54, neither applicant, nor the abstract by Euhus et al. disclose the amino acid sequence of UTAA.Thus the information concerning UTAA provided by Euhus et al. is indistinguishable from that of the claimed invention, due to the lack of structural information from both Euhus et al and applicant.

Furthermore, the immunological profile of the isolated UTAA taught by Euhus et al is the same as that of the claimed UTAA. Antibodies to UTAA are known, which have been used for detecting the presence of UTAA by Euhus et al, and Rote et al. In fact, such recognition of UTAA in patient urine, by patient sera antibodies, is used for the definition of UTAA. Said antibodies, which are from sera of patients, or from rodents, as taught by Euhus et al, (lines 8-9), have recognition of UTAA which is not any different from that of the claimed monoclonal antibody against the claimed UTAA. In other words, applicant does not disclose any specific

region of the claimed UTAA which is specifically recognized by the claimed monoclonal antibody, but not by patient sera antibodies, or by the monoclonal antibody taught by Euhus et al.

In summary, the isolated UTAA taught by Euhus et al is similar to the claimed UTAA, because the methods taught by Euhus et al for obtaining UTAA are routinely done in the art, and because UTAA taught by Euhus et al, and the claimed UTAA are recognized by the same antibody, have similar molecular weight, and are found from the same sources, i.e. urine and sera, of the same types of patients having the same tumors. Furthermore, the isolated UTAA taught by Euhus et al is indistinguishable from the claimed UTAA, because neither Euhus et al., nor applicant disclose the amino acid sequence of UTAA.

REJECTION UNDER 35 USC 103, NEW REJECTION

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or unobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 19, 62-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Euhus et al., *supra*, in view of Rote, NS et al., 1980, J Surgical Research, 29: 18-22, or Finck SJ et al, 1982, J Surgical Oncology, 21: 81-86, Pharmacia Fine Chemicals, Gel filtration, Theory and practice, 1980, pages 4, 14, 26-27, Pharmacia fine Chemicals, Ion exchange chromatography, Principles and methods, 1980, pages 3-7, 43-47, Ljungquist, S, 1977, JBC, 252(9): 2808-2814, and Goldenberg, 1982, US 4,348,376.

Claims 19, 62-79 are drawn to an isolated Urinary Tumor Associated Antigen (UTAA) subunit, which after reduction by beta-mercaptoethanol and separation by SDS-polyacrylamide gel electrophoresis (SDS-PAGE), exhibits a molecular weight of about 90 to 100 kD. Said UTAA is purified at least about 100-fold, or 105-fold over UTAA found in urine, and is present as at least about 0.6% of total protein in the original composition. Said UTAA has an isoelectric point

of about 6.1, is heat stable at 100^0 C, is about 95% or 99.5% free of immunoglobulin, and contains glycosidase-sensitive carbohydrates. Claims 19, 62-79 are also drawn to a pharmaceutical composition comprising said purified UTAA, and a pharmaceutical buffer, wherein said UTAA is present as at least about 0.63 ug/ml, or 1.4 ug/ml, or 36 ug/ml, or 40 ug/ml, or 100 ug/ml, or 200 ug/ml of buffer. Claims 19, 62-79 are further drawn to a method for inducing or enhancing in a subject the production of antibodies reactive with UTAA, comprising administering said purified UTAA. The observed enhancement of antibody production is about 2- to 5-fold.

Euhus et al. teach the isolation of urinary tumor asssociated antigen (U-TAA) from sera of melanoma patients. Euhus et al. also teach that because said antigen was detected in the urine of melanoma patients, using autologous and allogeneic antibody in ELISA, it was termed urinary tumor asssociated antigen . A monoclonal antibody to U-TAA is developed, and used in ELISA to detect U-TAA. Said U-TAA is isolated by dye ligand, and gel filtration chromatography, and DEAE anion exchange chromatography or 4.5% polyethylene glycol precipitation. The free U-TAA in serum has a molecular mass of 620 kD, which is separated into four bands in SDS-PAGE; two of which, 142 kD and 111 kD, correspond to those present in U-TAA in urine. The isolated U-TAA is free of IgG and IgM. Euhus et al. further teach that pure U-TAA antigen will provide valuable reagents for the immunoprognosis of human melanoma.

Euhus et al. do not teach that UTAA is purified at least about 100-fold, or 105-fold over UTAA found in urine, and is present as at least about 0.6% of total protein in the original

composition. Euhus et al. do not teach that said UTAA has an isoelectric point of about 6.1, is heat stable at 100^0 C, is about 95% or 99.5% free of immunoglobulin, and contains glycosidase-sensitive carbohydrates. Euhus et al. do not teach a pharmaceutical composition, wherein said UTAA is present as at least about 0.63 ug/ml, or 1.4 ug/ml, or 36 ug/ml, or 40 ug/ml, or 100 ug/ml, or 200 ug/ml of buffer. Euhus et al. do not teach a method for inducing or enhancing in a subject the production of antibodies reactive with UTAA, comprising administering said purified UTAA, wherein the observed enhancement of antibody production is about 2- to 5-fold.

Rote et al. teach tumor-associated antigens detected by autologus sera in urine of patients with solids neoplasms, using complement fixation assay. Unlike other tumor-related urinary antigens, the antigens taught by Rote et al induce a complement fixing antibody in the host, are heat stable at 100^0 C for 60 min. Said antigens are comprised of molecules of about $1x\ 10^6$ daltons, which could be dissociated into smaller subunits by treatment with 6 M urea.

Finck et al teach tumor-associated antigens found in urine of patient with colon carcinoma. Said antigen could be detected with complement fixation assay, using autologous serum as the antibody source. Said antigen has a molecular weight of >100,000 dalton, and is heat stable at 100^0 C (p.85).

Pharmacia Fine Chemicals teach how to purify proteins using gel filtration and ion exchange chromatography. Pharmacia teaches that "the separation of proteins in gel filtration depends on the different abilities of the various sample molecules to enter pores which contain the stationary phase. Very large molecules which never enter the stationary phase, move through the

chromatographic bed fastest" Smaller molecules are eluted in order of decreasing molecular size" (Gel filtration, page 4). The eluent is just a simple buffer solution, as shown in one example on figure 6, page 14 (Gel filtration). Furthermore, molecular weight standards are routinely used for calibrating the gel filtration column (Gel filtration, pages 26-27). It is well known in the art that molecular weight standards could be easily tagged with dye ligands for color detection on the column. Pharmacia also teaches methods of elution of proteins from ion exchange columns, including DEAE columns, using a continuous NaCL gradient (Ion exchange chromatography, pages 3-7, 43-47). Peaks of different proteins are separated by said continuous gradient elution, and thus could be detected.

Ljunquist teaches the purification of endonuclease IV by 3000-fold, using a combination of ammonium sulfate, gel filtration on Sephadex G-75, heat treatment, and DNA-cellulose.

US 4,348,376 teaches production of antibodies to the tumor antigen CEA, and the use of said antibodies for tumor localization and therapy.

The art establishes that it was possible at the time the invention was made to isolate UTAA from sera of melanoma patients. Said UTAA is termed urinary tumor associated antigen because it is detected in urine of melanoma patients. A subunit of said UTAA from sera is 111 kD in SDS-PAGE, corresponding those present in UTAA in urine. Although 111 kD is not 90 to 100 kD, it is well known in the art that molecular weight determination by SDS-PAGE, at high molecular weight range, is not very accurate, and could easily vary by 10%. As also shown by applicant's own data, the molecular weight of the claimed UTAA varies by about 10%. Thus the

111 kD UTAA taught by Euhus et al. could have a similar molecular weight as the claimed UTAA. The art also teaches the protocols for isolating UTAA, i.e. by gel filtration, and DEAE anion exchange columns. Although the abstract by Euhus et al do not describe in detail how to isolate UTAA using gel filtration, and DEAE anion exchange columns, it is a routine protocol in the art, as shown in the handbooks Pharmacia, or Ljungquist. In other words, proteins of different sizes are separated by gel filtration, using a simple buffer solution; and different proteins are separated by a DEAE column, eluted as different protein peaks, using a continuous salt gradient elution. The art further teaches how to detect UTAA, i.e. either by ELISA, which is a well known method in the art, or by complement fixation test, using autologous or allogeneic sera of melanoma patients. Thus the eluted peaks from gel filtration or DEAE column could be detected by either ELISA or by complement fixation test, using autologous or allogeneic sera of melanoma patients.

Therefore, it would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to purify UTAA from urine samples of melanoma patients, using the methods taught by Euhus et al, Pharmacia, and Ljungquist. Although isolated from sera of melanoma patients, the isolated UTAA, as taught by Euhus et al, is the same as the claimed UTAA, which is isolated from urine of melanoma patients, because UTAA is originally found in urine of melanoma patients, and because the molecular weight (111 kD) of a subunit of UTAA taught by Euhus et al. is not significantly different from that of the claimed UTAA, having a molecular weight from about 90 kD to about 100 kD. Furthermore, the isolated UTAA taught by

Euhus et al is free of IgG and IgM, and thus is at least 95% or 99.5% free of immunoglobulin. Although Euhus et al. do not specifically teach the degree of purification of UTAA, such degree of purification is expected, given similar protocols used by Euhus et al. and applicant. Once UTAA is isolated, it would have been obvious to dilute it or to concentrate it to various concentrations in a buffer. Moreover, the claimed properties of UTAA, i.e., an isoelectric point of about 6.1, being heat stable at 100^0 C, and containing glycosidase-sensitive carbohydrates are inherent properties of UTAA.

It would have been obvious to use UTAA for inducing or enhancing the production of antibodies reactive to UTAA, because Euhus et al suggest the use of the isolated UTAA for the immunoprognosis of human melanoma, and because it is well known in the art that tumor antigens are used for the production of antibodies, and antibodies to tumor are used for treating tumors (see for example, US 4,348,376). Furthermore, administering the same antigen UTAA is expected to give similar 2- to 5-fold enhancement in the production of antibodies reactive to UTAA, because the specification does not disclose any specific method of production of antibodies which is different from routine methods of production of any antibody known in the art.

One of ordinary skill in the art would have been motivated to isolate UTAA from urine of melanoma patients, and to use said isolated UTAA for inducing or enhancing the production of antibodies reactive to UTAA, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to isolate UTAA from urine of melanoma patients, and to use

said isolated UTAA for inducing or enhancing the production of antibodies reactive to UTAA for the immunoprognosis of melanoma.

Claims 73-79, drawn to a pharmaceutical composition, read on UTAA in a carrier, i.e. water. The language pharmaceutical composition is not given any patentable weight in applying prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 7:00am to 3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2297. The fax phone number for this Group is (703) 308-4227.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**lila.feisee@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless **the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122.** This is more clearly set

forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

October 20, 1997

Lila Feisee
Supervisory Patent Examiner
Group 1800